CRYSTALLOGRAPHIC STRUCTURE OF THE ANDROGEN RECEPTOR LIGAND BINDING DOMAIN

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Field of Invention This application claims benefit under 35 U.S.C. Section 119(e) to US provisional application 60/159,394, filed October 14, 1999.

The present invention relates to compositions and crystals of androgen receptor ligand binding domain optionally in complex with its ligand. This invention also relates to methods of using the structure coordinates of the androgen receptor ligand binding domain /ligand complex to solve the structure of similar or homologous proteins or protein complexes. This invention also relates to methods for designing and selecting ligands that bind to the androgen receptor and methods of using such ligands.

Background of the Invention

The androgen receptor (AR) is a member of the steroid nuclear-receptor superfamily of ligand-dependent transcription factors. The binding of androgen to AR initiates the gene activation required for male sex development.

AR is an important target primarily in two drug discovery areas. In oncology drug discovery, inhibitors (antagonists or partial antagonists) of androgen receptor function are useful for treatment of anti-androgen refractory prostate cancer. In metabolic diseases drug discovery, agonists or partial agonists to the androgen receptor in muscle are useful to treat age-related diseases.

As with the other members of the steroid receptor family, AR has several functional domains including a DNA binding domain (DBD), and a 261 residue ligand-binding domain (LBD) (Mw = 30,245 Da) which contains the androgen binding site, and is responsible for switching on the androgen function.

Development of synthetic ligands that specifically bind to androgen receptors has been largely guided by trial and error method of drug design despite the importance of the androgen receptor in physiological processes and medical conditions such as prostate cancer and modulation of reproductive organ modulation. Previously, new ligands specific for androgen receptors were discovered in the absence of information on the three dimensional structure of the androgen receptor with a bound ligand. Before the present invention, researchers were